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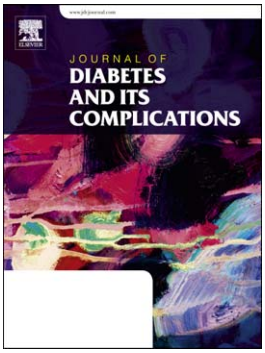


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# Treatment with GLP1 receptor agonists reduce serum CRP concentrations in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials

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**Running title:** Glucagon-like peptide-1 receptor agonist and C-reactive protein

**Conflict of interest:** The authors have no conflict of interest.

**Abstract:**

**Aim:** To undertake a systematic review and meta-analysis of randomized controlled trials of the effect of Glucagon-like peptide-1 receptor agonist (GLP-1 RAs) therapy on serum C-reactive protein (CRP) concentrations.

**Method:** PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched for the period up until March 16 2016. Prospective studies evaluating the impact of GLP-1 RAs on serum CRP were identified. A random effects model (using the DerSimonian-Laird method) and generic inverse variance methods were used for quantitative data synthesis. Sensitivity analysis was conducted using the leave-one-out method. Heterogeneity was quantitatively assessed using the $I^2$ index. Random effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the impact of potential moderator.

International Prospective Register for Systematic Reviews (PROSPERO) number CRD42016036868.

**Results:** Meta-analysis of the data from 7 treatment arms revealed a significant reduction in serum CRP concentrations following treatment with GLP-1 RAs (WMD –2.14 (mg/dL), 95% CI -3.51, –0.78, P=0.002; $I^2$ 96.1%). Removal of one study in the meta-analysis did not change the result in the sensitivity analysis (WMD –2.14(mg/dL), 95% CI -3.51, –0.78, P=0.002; $I^2$ 96.1%), indicating that our results could not be solely attributed to the effect of a single study. Random effects meta-regression was performed to evaluate the impact of potential moderator on the estimated effect size. Changes in serum CRP concentration were associated with the duration of treatment (slope –0.097, 95% CI –0.158, -0.042, P<0.001).

**Conclusions:** This meta-analysis suggests that GLP-1 RAs therapy causes a significant reduction in CRP.

**Keywords:** meta-analysis, Glucagon-like peptide-1 receptor agonist, C-reactive protein.

**Word count:** 233

**Introduction:**

Obesity and T2DM are both associated with an increased risk of cardiovascular disease (CVD) These conditions are also now recognised as having an inflammatory component [1]. A number of cytokines and inflammatory signalling pathways have been shown to be involved in the development of CVD, as indicated by increased serum levels of several inflammatory biomarkers, including: tumour necrosis factor-a (TNF-a), C reactive protein (CRP), high molecular weight adiponectin (HMW-adiponectin), and interleukin (IL)-6 [2]. The potential role of inflammation in the complications of obesity is offering further insight into the relationship between T2DM and CVD has led to a greater interest on specific therapeutic targeting. Glucagon-like peptide-1 (GLP-1) is a gut hormone, secreted from the intestine in response to meal ingestion, which stimulates insulin secretion and inhibits glucagon release in a dose-dependent fashion [3]. GLP-1 can suppress appetite, food intake, decelerate gastric emptying and induce satiety, so it plays an important role in the regulation of blood glucose [4, 5]. GLP-1 receptor agonists (GLP-1 RAs) include exenatide, liraglutide, albiglutide, taspoglutide, lixisenatide. Treatment with GLP-1 RAs improve insulin resistance and glucose homoeostasis in patients with Type 2 DM [6, 7]. The use of these agents, also have a low risk of hypoglycemia because of their mode of action. Exenatide and liraglutide are currently successfully being employed in the treatment of Type 2 DM [8]. However, the data on the effect of GLP-1 RAs on serum CRP is inconsistent. Hence the aim of this study was to assess the reported effects of GLP-1 RAs on serum CRP by systematically reviewing the existing randomize control trials.

**Methods**

***Literature search strategy***

A systematic review was undertaken according to the international referred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) Guidelines [9, 10]. The primary exposure of interest was GLP-1 RAs use and the primary outcome was the change in CRP concentration status subsequent to GLP-1 RAs use. The secondary aim of this study was to assess the effect of duration of GLP-1 RAs therapy on serum CRP concentrations. We searched multiple databases including PUBMED, Medline, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), Web of Science, Gray Literature sources, SCOPUS, and clinicaltrial.gov registry until March 2016, for both published and unpublished studies on changes in serum CRP concentration in relation to treatment with GLP-1 RAs. We used a combination of relevant search terms (Supplementary Table 1). No language restriction was applied. Additionally, we hand-searched the reference list of eligible articles and contacted authors for missing information/clarifications where relevant. Results of unpublished trials were retrieved, if available, from www.clinicaltrials.gov, or www.clinicalstudyresults.org, as well as Food and Drug Administration and European Medicines Agency (EMEA, www.ema.europa.eu) reviews of approved drugs. All those sources were also used to complete information on results of published trials, when not reported in publications (including the primary trial publications, and subsequent reviews and/or pooled analyses reporting data on individual trials). The full text of studies meeting the inclusion criteria retrieved and screens to determine eligibility by two reviewers (MM, EE). Disagreements resolved through discussions between reviewers until consensus reached. International Prospective Register for Systematic Reviews (PROSPERO) number CRD42016036868.

***Selection criteria***

We included prospective studies evaluating the effect of GLP-1 RAs use on serum CRP levels. Eligible studies had to meet following criteria: (1) a controlled trial with either parallel or crossover design; (2) presentation of sufficient information on CRP concentrations at baseline and at the end of follow-up in each group or providing the mean change during follow-up. Unclear studies, poorly described and only abstract papers were excluded. Narrative reviews, comments, opinion pieces, methodological, editorials, letters or any other publications lacking primary data and/or explicit method descriptions, were also excluded. After removal of duplicates, two investigators (MM & EE) independently screened studies by title, abstract and full text as appropriate for inclusion. The agreement between the two investigators was excellent (Kappa index: 0.91; p<0.001)). Disagreements were resolved at a meeting between reviewers prior to selected articles being retrieved (a flow chart is available in supplementary Figure 1). For multiple publications from the same study, only the most complete reports were included.

***Data extraction*** **and management:**

Two reviewers entered data onto a purpose-designed data extraction form and independently summarised what they considered to be the most important results from each study. These summaries compared any differences of opinion resolved by discussion and consultation with a third reviewer. Any further calculations on study data considered necessary was conducted by the first reviewer and checked by the second reviewer. The quality of trials was assessed using some of the parameters proposed by Jadad et al, [11]First author, year, differential interventions in study groups, duration of interventions (week), sample size, number of men (%), mean age and trials quality were summarized in table 1.

**Quality Assessment*:***

A systematic assessment of bias in the included RCTs was performed using the Cochrane criteria [12]. The items used for the assessment of each study were the following: adequacy of random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, handling of drop-outs (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of 'yes' indicated low risk of bias, while 'no' indicated high risk of bias. Labelling an item as 'unclear' indicated an unclear or unknown risk of bias.

**Quantitative data synthesis:**

A random effects model (using the DerSimonian– Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of studies in terms of demographic characteristics of populations being studied and also differences in study design and type of statin being studied [13]. Heterogeneity was quantitatively assessed using the $I^2$ index. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the leave-one-out method, i.e. removing one study each time and repeating the analysis [14-16]. When the outcome measure was reported as median and range (or 95% confidence interval [CI]), mean and standard deviation (SD) values were estimated using the method described by Hozo et al. [17]. Where standard error of the mean (SEM) was only reported, the SD was estimated using

the following formula: SD = SEM × square root (n), where n is the number of subjects. If the outcome measures were reported in median and $25^{th}$-$75^{th}$ percentiles (P25-P75), mean and standard SD values were estimated using a method previously defined [17]. To convert P25-P75 into a minimum–maximum range, the following equations were used: maximum = median + 2 *(P75-median) and minimum = median - 2 * (median-P25), where P25, and P75 are the $25^{th}$ and $75^{th}$ percentiles, respectively. All values were collated in percentage of change. SDs of the mean difference were estimated using the following formula: SD = square root $[(SD_{pretreatment})^2 + (SD_{posttreatment})^2 \_ (2R * SD_{pretreatment} * SD_{posttreatment})]$. Because the pretest–posttest correlation coefficients (r) were not reported in studies, an r value of 0.5 was assumed through this meta-analysis, as this value was a conservative estimate for r which ranges between 0 and 1 [18]. In order to check if the r value could alter the results of the meta-analysis, sensitivity analyses were performed by repeating the analysis with r values of 0.2, 0.3, 0.7 and 0.8. The results showed the robustness of the pooled estimate with different r values.

**Meta-regression**

Random effects meta-regression was performed using the unrestricted maximum likelihood method to evaluate the association between calculated WMD and potential moderator, duration of treatment with GLP-1 RAs.

**Publication bias**

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie 'trim and fill' and 'fail-safe N' methods were used to adjust the analysis for the effects of publication bias[19]. Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V3 software (Biostat, NJ)[20].

**Results**

***Summary of searches and study selection process***

The search strategy identified 532 citations. Three hundred and ninety records remained after removing duplicates. After initial screening based on titles and abstracts, 43 articles remained for further evaluation. 36 full- text articles were excluded for the following reasons: 1- They were non-human studies, genetic, or molecular studies (n=30); 2- They were reviews or editorial articles (n=6). Study selection with flow diagram based on the PRISMA guidelines shown in supplementary figure 1.

***Characteristics of the included studies***

The remaining 7 studies met our inclusion criteria and were included in the meta-analysis. Two of these studies were prospective cohort studies and the others are randomized clinical trials. Publication years were between 2010 and 2014, and the duration of the studies ranged from 8 weeks to 52 weeks. 2 trials compared GLP-1 agonist (exenatide) with metformin on non-diabetic individuals with abdominal obesity and either IFG, elevated HbA1c or IGT [21] and withT2DM and concomitant non-alcoholic fatty liver disease (NAFLD) [22], respectively. One trial compared GLP-1 agonist (exenatide) with placebo on a background of basal insulin with oral anti-diabetic drugs [23]. One study compared GLP-1 agonist (exenatide) with glibenclamide on patients

with uncontrolled type 2 diabetes mellitus receiving therapy with metformin [24]. One trial compared GLP-1 agonist (exenatide) with insulin glargine on metformin-treated patients with type 2 diabetes [25]. One study compared GLP-1 agonist (liraglutide) versus placebo on glucose-tolerant patients with plaque psoriasis [26]. At the end, one trial investigated effect of exenatide therapy in obese people with type 2 diabetes mellitus (T2DM) and hypertension after laparoscopic Roux-en-Y gastric bypass (RYGB) surgery [27].

Participants in two studies were only female, while the proportion of men in other studies ranged from 24% [21] to 65% [27]. Studies were from countries including the Denmark (one study), United States of America (one study), Italy (one study), China (three study) and Netherlands (one study). The number of participants included in studies ranged from 20 [26] to 117 [22]. The range of age participants was from 18 years [24] to 69 years [21]. Moreover, each of these studies had its own inclusion criteria which are listed in Table 1.

**Risk of Bias Assessment**

There is unclear risk of bias in some of items including allocation concealment, blinding of participants and personnel. All of the studies had a low risk of bias according to selective outcome reporting. Details of the quality of bias assessment are shown in supplementary table 2.

***Pooled estimate of* GLP-1 RAs treatment *on* CRP**

The pooled estimate (weighted mean difference) of the effect of GLP-1 RAs treatment on CRP levels was (WMD –2.14 (mg/dL), 95% CI -3.51, –0.78, N=7 studies, heterogeneity P=0.002; $I^2$ 96.1%) across all studies.

***Sensitivity analysis***

In leave-one-out sensitivity analyses, the pooled effect estimates remained similar across all studies (WMD –2.14 (mg/dL), 95% CI -3.51, –0.78, N=7 studies, heterogeneity P=0.002; $I^2$ 96.1%), fig 1.

**Meta-regression:**

Random effects meta-regression was performed to evaluate the impact of potential moderator on the estimated effect size. Changes in serum CRP concentration were associated with the duration of treatment (slope –0.097, 95% CI –0.158, -0.042, P<0.001) (Figure 2).

***Pooled estimate of* GLP-1 RAs treatment on plasma adiponectin:**

Meta-analysis of the data from 3 treatment arms revealed a significant change in plasma adiponectin concentration following treatment with GLP-1 RAs (WMD 0.64, 95% CI 0.38, 0.89, P<0.001; $I^2$ 46%). This effect was robust in the sensitivity analysis (Figure 3).

**Publication bias**

The funnel plot of standard error vs. effect size (mean difference) was asymmetric and suggested potential publication bias, fig4. Moreover, the presence of publication bias was suggested by Egger's linear regression (intercept = -10.6, standard error = 5.47; 95% CI = -24.7, 3.42, t = 1.96, df = 5.00, two-tailed P = 0.109). However, Begg's rank correlation test (Kendall's Tau with continuity correction =-0.50, z = 1.65, two tailed P value =0.098) did not indicate significant publication bias. After adjustment of effect size for potential publication bias using the 'trim and fill' correction, no potentially missing studies were imputed in the funnel plot, hence no difference on effect size than the initial estimate (WMD –0.99, 95% CI -1.22, –0.76) (Figure 3).

The 'fail-safe N' test showed that 243 studies would be needed to bring the WMD down to a non- significant (P > 0.05) value.

**Discussion**

The GLP-1 RAs are a novel class of glucose-lowering drugs which have been shown to improve glycaemic control and promote weight loss in clinical studies of patients with Type 2DM and obesity. Nevertheless, little is known about the effects of chronic treatment with GLP-1 receptor agonist on inflammatory markers that are known to be associated with obesity or type 2 diabetes. We have reviewed studies that have investigated the effects of GLP-1 receptor agonist on the inflammatory biomarker CRP. Meta-analysis revealed that these agonists have a potentially beneficial effect on serum CRP concentrations, as we observed a significant reduction in serum CRP concentration following treatment with GLP-1 RAs. The GLP-1 RAs used for most of these studies was exenatide, which is a synthetic analogue of exendin-4, a 39-amino-acid agonist of GLP-1 receptor. It can promote glucose-dependent insulin secretion, inhibit inappropriate secretion of glicentin, delay gastric emptying, and suppress appetite to reduce blood glucose and body weight [31]. in a recent study investigating the effects of three different dose of liraglutide (0.6 mg, 1.2 mg and 1.8 mg) in patients with type 1 diabetes mellitus; serum CRP concentrations fell significantly by 15 ± 6% (from 3.01± 0.92 to2.53 ± 0.83 g/L, P < 0.05) in the liraglutide 1.2-mg group and by 19±8% (from 3.53±0.67 to 2.57±0.52 g/L, P < 0.05) in liraglutide 1.8 mg group [32]. Furthermore, Bunck et al showed that exenatide was superior to insulin glargine in improving the risk factors of cardiovascular diseases such as adiponectin and CRP [25]. It has been shown that there is a highly significant association between elevated CRP and glucose control in T2DM [33]. We also reviewed the effect of GLP-1 RAs on serum adiponectin in these studies. Adiponectin is another inflammatory marker, derived from adipose tissue that has been shown to be involved in the obesity and T2DM complicated by cardiovascular diseases. Three studies in this systematic review also evaluated serum adiponectin concentration after treatment with GLP-1 RAs agonist in patients [22, 25, 27]. They reported GLP-1 RAs had a significant effect on increasing serum adiponectin concentrations. Our analysis also revealed a significant change in plasma adiponectin concentrations following treatment with GLP-1 RAs. TNF-a is a major negative regulator that can block fatty acid oxidation and glucose uptake and induce metabolic disorders [34]. It hypothesized, adiponectin with its antagonistic effects on TNF-a, may improve diabetes, hypertension, apoptosis, and atherosclerosis [35]. The Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial showed conclusive data regarding the cardiovascular safety of liraglutide relative to standard of care for a global population of patients with T2DM[36].

In conclusion, GLP-1 RAs, appear to reduce serum CRP and increase serum adiponectin concentrations and may therefore attenuate the inflammatory state, and hence reduce the risk of CVD, and the degree of insulin resistance in patients with diabetes. Furthermore, the reduction in inflammatory markers such as CRP may also indicate that these agents reduce the risk of diabetic complications, including nephropathy and atherosclerosis.

**Limitation:**

Although we believe that the present meta-analysis provides useful information, there are some potential limitations that need to be addressed. First, as with any meta-analysis, internal validity relies on the quality of individual studies. Several limitations of this meta-analysis should be noted. Firstly, the majority of the studies finally included in the analysis had relatively small sample sizes, potentially leading to publication bias and overestimation of treatment effects, because smaller trials might be methodologically less robust and are prone to report larger effect sizes[37, 38]. Therefore, the present meta-analysis may have been underpowered to detect a true effect.

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| Study name | Std diff in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|
| A. Faurschou | -0.006 | 0.449 | 0.202 | -0.887 | 0.875 | -0.013 | 0.990 |
| Aaron S Kelly | 0.000 | 0.283 | 0.080 | -0.554 | 0.554 | 0.000 | 1.000 |
| G. Derosa | -3.333 | 0.287 | 0.082 | -3.896 | -2.771 | -11.613 | 0.000 |
| Hui Fan | -0.499 | 0.190 | 0.036 | -0.872 | -0.126 | -2.622 | 0.009 |
| Jin-dan Wu | -2.837 | 0.591 | 0.349 | -3.995 | -1.678 | -4.800 | 0.000 |
| MATHIJS C. BUNCK | -2.000 | 0.319 | 0.102 | -2.625 | -1.375 | -6.271 | 0.000 |
| Ziwen Liang | -6.743 | 0.618 | 0.382 | -7.954 | -5.531 | -10.910 | 0.000 |
| | -2.148 | 0.696 | 0.484 | -3.512 | -0.784 | -3.086 | 0.002 |

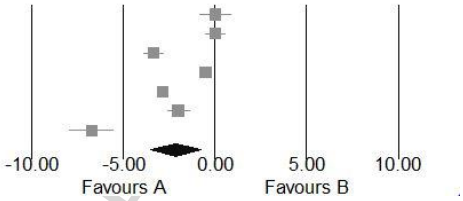


Figure 1

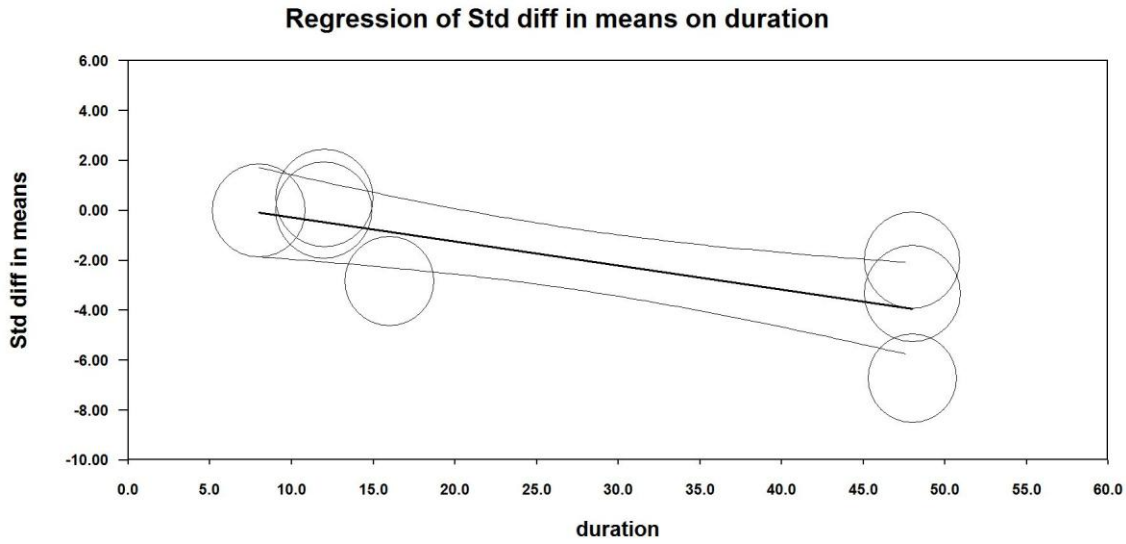


Figure 2

| Study name | Std diff in means | Standard error | Variance | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|
| Hui Fan | 0.631 | 0.192 | 0.037 | 0.255 | 1.007 | 3.287 | 0.001 |
| MATHIJS C. BUNCK | 0.284 | 0.262 | 0.069 | -0.229 | 0.797 | 1.086 | 0.277 |
| Ziwen Liang | 0.989 | 0.253 | 0.064 | 0.492 | 1.485 | 3.902 | 0.000 |
| | 0.640 | 0.132 | 0.017 | 0.381 | 0.899 | 4.845 | 0.000 |

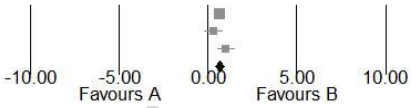


Figure 3

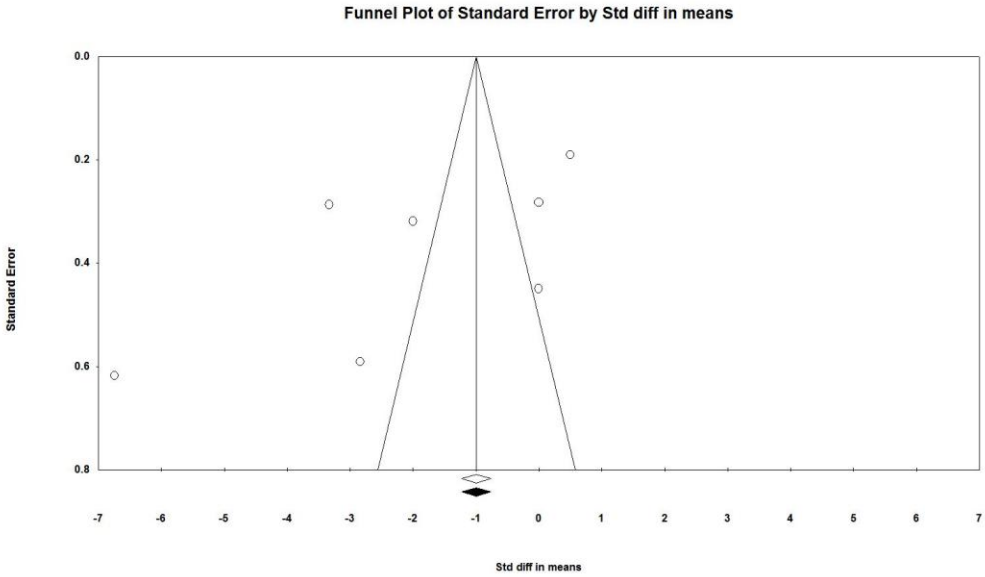


Figure 4

| Table 1: Characteristics of included trials | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Authors ,** | **year** | **Country** | **Differential interventions in study groups** | **Inclusion criteria** | **Duration of intervention** | **Sample size** | **Percent of Men** | **Mean age** | **Quality** |
| **A. Faurschou** | 2014 | Denmark | liraglutide vs placebo | plaque psoriasis with a psoriasis area and severity index (PASI) of at least 8, (ii) no treatment, or treatment of psoriasis with the same medication for at least 3 months prior to inclusion, (iii) a steady bodyweight over a 3-month period with a body mass index (BMI) >25 kg/m2. | 8 week | 20 | ND | 48-54 | 4 |
| **Aaron S Kelly** | 2012 | USA | Exenatide vs metformin | …….. | 3 month | 50 | 24% | 58.5 ± 10.0 | 2 |
| **G. Derosa** | 2010 | Italy | Exenatide vs glibenclamide | poor glycemic control (expressed as HbA1c level >8.0%) and overweight (body mass index [BMI] 25 and <30 kg=m2) receiving therapy with metformin at the mean dosage of 1,500500mg=day | 12 month | 116 | | ≥18 years | 1 |
| **Hui Fan** | 2013 | China | exenatide vs metformin | T2DM concomitant with NAFLD, poor glucose control (FBG: 6.0-10.0 mmol/L or HbA1c: 7-9%), no acute complications or | 12 week | 117 | 56.4% | 52.35 | 1 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | severe chronic complications of DM | | | | | |
| **Jin-dan Wu** | 2011 | China | Exenatide vs placebo | (1) insulin injection for more than 1 week in the previous 3 months; (2) severe coronary disease history in the previous 1 year; (3) blood creatine ≥133 mmol/L for men and ≥106 mmol/L for women; and (4) glutamate-pyruvate transaminase ≥2.5 times greater than the normal value | 16 week | 23 | 39.1% | Exenatide Group; 57±10 Placebo group; 54±9.5 | 3 |
| **MATHIJS C. BUNCK** | 2010 | Netherlands | exenatide vs insulin glargine | ND | 12 month | 69 | ND | ND | 1 |
| **Ziwen Liang** | 2013 | China | Exenatide | (1) obesity (body mass index [BMI] > 28 kg/m2) in accordance with the WHO Asia-Pacific classification for obesity [9]; (2) T2DM with hypertension of 5–10 years with hypertension defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic (DBP) ≥90 mmHg as per 1999 WHO/ISH criteria; (3) insulin therapy in combination with oral | 12 month | 108 | 64.8% | Exenatide Group ; 50.94 ± 5.89 | 2 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | administration of drugs for 12 months; (4) glycated hemoglobin (HbA1c) > 7%; (5) age: 30–60 years; (6) seronegative for antibodies against insulin, islet cells and glutamic acid decarboxylase (GAD); (7) C-peptide level ≥0.3 mg/L. | | | | | |